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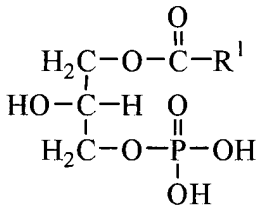
NY_MAIN 236547 v1

Application No: (National Phase of PCT Application No. PCT/JP00/05542 filed August 18, 2000)
Attorney Docket No. 02139.000029

VERSION WITH MARKINGS TO SHOW CHANGES MADE TO CLAIMS

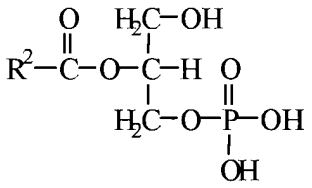
5. (Amended) The hair-growing agent according to [any of] Claim[s] 1 [to 4] or 2, wherein the lysophosphatidic acids are compounds represented by formula (I):



(I)

(wherein R^1 represents alkyl, alkenyl or alkynyl).

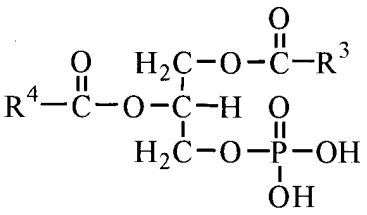
6. (Amended) The hair-growing agent according to [any of] Claim[s] 1 [to 4] or 2, wherein the lysophosphatidic acids are compounds represented by formula (II):



(II

(wherein R^2 has the same significance as the above R^1).

7. (Amended) The hair-growing agent according to [any of] Claim[s] 1 [to 4] or 2, wherein the phosphatidic acids wherein the fatty acid residue moiety consists only of straight-chain fatty acid residues having an even number of carbon atoms are compounds represented by formula (III):



(III)

(wherein R^3 and R^4, which may be the same or different, each represents straight-chain alkyl having an odd number of carbon atoms, straight-chain alkenyl having an odd number of carbon atoms, or straight-chain alkynyl having an odd number of carbon atoms).

11. (Amended) The hair-growing agent according to Claim 9 [or 10], further comprising a protein kinase C-specific inhibitor or a pharmaceutically acceptable salt thereof.

13. (Amended) The hair-growing agent according to Claim 8[, 11] or 12, wherein the protein kinase C-specific inhibitor is one or more members selected from the group

consisting of calphostin C, hexadecylphosphocholine, palmitoyl-DL-carnitine and polymyxin B.

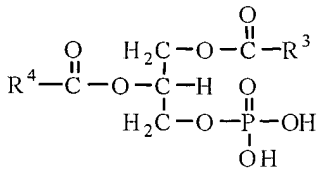
14. (Amended) The hair-growing agent according to any of Claims 9 [to 13] or 12, further comprising tocopherol.

16. (Amended) The hair-growing agent according to Claim 8[, 14] or 15, wherein the tocopherol is one or more members selected from the group consisting of dl-α-tocopherol, d-α-tocopherol, dl-α-tocopherol acetate, d-α-tocopherol acetate and dl-α-tocopherol nicotinate.

17. (Amended) The hair-growing agent according to any of Claim[s 8 to 16] 8, 9, 11, 12, 15, 30, 33, 36, 39 or 42, wherein the [phosphatidic acids are the phosphatidic acids according to Claim 1] fatty acid residue moiety consists only of straight-chain fatty acid residues having an even number of carbon atoms.

18. (Amended) The hair-growing agent according to Claim 17, wherein the

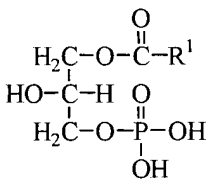
[phosphatidic acids are the phosphatidic acids according to Claim 7] fatty acid residue moiety consists only of straight-chain fatty acid residues having an even number of carbon atoms are compounds represented by formula (III):



(III)

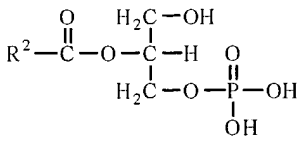
(wherein R^3 and R^4, which may be the same or different, each represents straight-chain alkyl having an odd number of carbon atoms, straight-chain alkenyl having an odd number of carbon atoms, or straight-chain alkynyl having an odd number of carbon atoms).

19. (Amended) The hair-growing agent according to any of Claims [8 to 16] 8, 9, 11, 12, 15, 30, 33, 36, 39 or 42 wherein the lysophosphatidic acids are [the lysophosphatidic acids according to Claim 5 or 6] compounds represented by formula (I):



(I)

(wherein R^1 represents alkyl, alkenyl or alkynyl), or compounds represented by formula (II):



(II)

(wherein R^2 has the same significance as the above R^1).

20. (Amended) The hair-growing agent according to any of Claims 8 [to 19], 9, 12 or 15, which does not substantially comprise minoxidil.

21. (Amended) The hair-growing agent according to [any of] Claim[s 8 to] 20, wherein the content of one or more members selected from the group consisting of lysophosphatidic acids and phosphatidic acids is 0.01 to 5.0%.

22. (Amended) The hair-growing agent according to [any of] Claim[s 8 to] 20, wherein the content of one or more members selected from the group consisting of lysophosphatidic acids and phosphatidic acids is 0.01 to 1.0%.

VERSION WITH MARKINGS TO SHOW CHANGES MADE TO SPECIFICATION

The paragraph at page 7, lines 3-4 have been amended as follows:

(20) The hair-growing agent according to any of the above (8) to (19), which does not substantially comprise minoxidil.

The paragraph starting at page 8, line 14 and ending at page 9, line 23 has been amended as follows:

The lysophosphatidic acids to be used in the present invention may be any lysophosphatidic acids. The phosphatidic acids wherein the fatty acid residue moiety consists only of straight-chain fatty acid residues having an even number of carbon atoms to be used in the present invention include all such phosphatidic acids. The straight-chain fatty acid residues having an even number of carbon atoms [of the above fatty acid residues] include[s] those having 2 to 24, preferably 8 to 18 carbon atoms, such as ethanoyl, butanoyl, hexanoyl, octanoyl, decanoyl, dodecanoyl, tetradecanoyl, hexadecanoyl, octadecanoyl, eicosanoyl, docosanoyl, tetracosanoyl, 2-butenoyl, 3-butenoyl, 3-hexenoyl, 5-hexenoyl, hexadienoyl, octenoyl, decenoyl, dodecenoyl, tetradecenoyl, hexadecenoyl, octadecenoyl, butynoyl, hexynoyl, octynoyl, decynoyl,

dodecynoyl, tetradecynoyl, hexadecynoyl, octadecynoyl and tetradec-4-en-8-ynoyl. Of the above lysophosphatidic acids, and phosphatidic acids wherein the fatty acid residue moiety consists only of straight-chain fatty acid residues having an even number of carbon atoms, preferred are compounds represented by formula (I). Examples of the lysophosphatidic acids are monoacetyl lysophosphatidic acid, monopropionyl lysophosphatidic acid, monobutanoyl lysophosphatidic acid, monopentanoyl lysophosphatidic acid, monohexanoyl lysophosphatidic acid, monoheptanoyl lysophosphatidic acid, monooctanoyl lysophosphatidic acid, monononanoyl lysophosphatidic acid, monodecanoyl lysophosphatidic acid, monoundecanoyl lysophosphatidic acid, monolauroyl lysophosphatidic acid, monotridecanoyl lysophosphatidic acid, monomyristoyl lysophosphatidic acid, monopentadecanoyl lysophosphatidic acid, monopalmitoyl lysophosphatidic acid, monoheptadecanoyl lysophosphatidic acid, monostearoyl lysophosphatidic acid and monooleoyl lysophosphatidic acid. Examples of the phosphatidic acids wherein the fatty acid residue moiety consists only of straight-chain fatty acid residues having an even number of carbon atoms are dioleoyl phosphatidic acid, dimyristoyl phosphatidic acid, dipalmitoyl phosphatidic acid, dilauroyl phosphatidic acid, dioctanoyl phosphatidic acid, didecanoyl phosphatidic acid, distearoyl phosphatidic acid, arachidonoylstearoyl phosphatidic

acid, 1-oleoyl-2-acetyl phosphatidic acid, 1-lauroyl-2-acetyl phosphatidic acid, 1-myristoyl-2-acetyl phosphatidic acid, 1-palmitoyl-2-acetyl phosphatidic acid, 1-stearoyl-2-acetyl phosphatidic acid and 1-palmitoleoyl-2-acetyl phosphatidic acid.

The paragraph at page 14, lines 24-33 have been amended as follows:

Grape-derived proanthocyanidin can be extracted and purified according to the method described in Acta Dermato Venereologica, 78, 428-432 (1998) or a similar method. Procyanidin B-1 [epicatechin-(4β→8)-catechin], procyanidin B-2 [epicatechin-(4β→8)-epicatechin], procyanidin B-3 [catechin-([4β] **4α**→8)-catechin] and procyanidin C-1 [epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin] can be extracted and purified according to the method described in The Journal of Investigative Dermatology, 112, 310-316 (1999) or a similar method.

The paragraph at page 19, lines 9-19 have been amended as follows:

Examples of the surfactants are polyoxyethylene (60) hardened castor oil, polyoxyethylene (8) oleyl ether, polyoxyethylene (10) oleyl ether, polyoxyethylene (10) monooleate, [polyoxyethylene (30) glyceryl monostearate], sorbitan monostearate,

polyoxyethylene (30) glyceryl monostearate, polyoxyethylene (20) sorbitan monooleate, sucrose fatty acid esters, hexaglycerin monooleate, hexaglycerin monolaurate, polyoxyethylene reduced lanolin, polyoxyethylene (20) lanolin alcohol, polyoxyethylene (25) glyceryl pyroglutamate isostearate, and N-acetylglutamine isostearyl ester.

The paragraph at page 21, lines 34-36 have been amended as follows:

Grape-derived proanthocyanidin was produced according to the method described in Acta Dermato Venereologica, 78, 428-432 (1998) [or a similar method].

The paragraph at page 22, lines 18-20 have been amended as follows:

Procyanidin B-2 was produced according to the method described in The Journal of Investigative Dermatology, 112, 310-316 (1999) [or a similar method].

The paragraph at page 23, lines 1-3 have been amended as follows:

Procyanidin C-1 was produced according to the method described in The Journal of Investigative Dermatology, 112, 310-316 (1999) [or a similar method].

Table 1 at page 27 has been amended as follows:

Table 1

Test Compound	PKC-IC_{50} [(μM)] μmol/l	PKA-IC_{50} [(μM)] μmol/l	PKA-IC_{50}/ [PKC-IC50] μmol/l
Calphostin C	0.05	>50	>1000
Hexadecyl-phosphocholine	94	>1000	>10.6
Palmitoyl-DL-carnitine	230	>1000	>4.3
Polymyxin B	2.6	>1000	>384

The paragraph starting at page 31, line 12 and ending at page 32, line 3 has been amended as follows:

Nine-weeks-old male C3H/HeSlc mice whose hair cycle was in the telogen were divided into groups each consisting of 4 or 5 mice. Hair on the back of each mouse was shaven using electric hair clippers and an electric shaver. Then, the compositions prepared in Examples 1-[14]13 were applied on the shaven part in an amount of 200 μl once per day. To the mice of control groups were applied compositions 2 and 16 respectively in the same manner.

The paragraph starting at page 32, line 14 and ending at page 33, line 11 has been amended as follows:

Table 3 (1) [Growth] Hair growth-promoting effect of lysophosphatidic acid on mouse [hair follicle]

Composition	Rate of increased hair-grown area (%)
2 (Control group)	0
1	35
3	60
4	45
5	64
6	51
7	67
8	57
9	68
10	60
11	73
12	63
13	60
14	45

Table 3 (2) [Growth] Hair growth-promoting effect of phosphatidic acids on mouse [hair follicle]

Composition	Rate of increased hair-grown area (%)
16 (Control group)	0
15	44
17	51
18	40
19	55
20	44
21	58
22	46
23	52
24	39
25	41

As shown in Table 3, the hair-growing agents comprising lysophosphatidic acid or phosphatidic acid of the present invention exhibited a significant hair growth-promoting effect on mouse [hair follicles]. The hair growth-promoting effect of proanthocyanidin, protein kinase C-specific inhibitors and tocopherol on hair follicles was reinforced by using them together with the lysophosphatidic acid.